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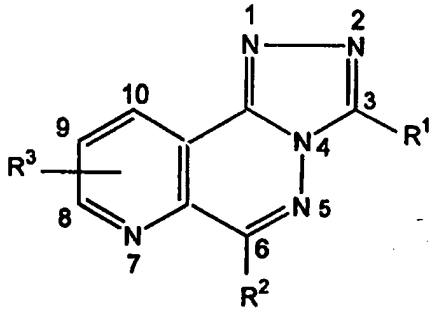
(54) Title: 1,2,4–TRIAZOLO[4,3–B]PYRIDO[3,2–D]PYRIDAZINE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

Heterocyclic compounds of formula (I), wherein R^1 represents a hydrogen atom or a $-(CH_2)_m-Y$ group, wherein m is an integer from 0 to 4 and Y represents an alkyl, haloalkyl, alkoxy, alkoxycarbonyl, C_3–C_7 cycloalkyl, norbornyl or phenylalkenyl group, or an aromatic group which aromatic group Y may optionally be substituted by one or more halogen atoms; R^2 represents an aromatic group which aromatic group may optionally be substituted by one or more halogen atoms or alkyl, alkoxy, C_3–C_6 cycloalkoxy, methylenedioxy, nitro, dialkylamino or trifluoromethyl groups; and R^3 represents a hydrogen or halogen atom or an alkyl group, and pharmaceutically acceptable salts thereof, processes for preparing the same. The compounds are phosphodiesterase 4 inhibitors.



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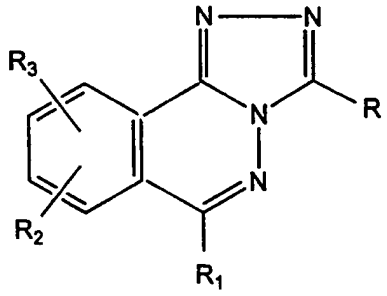
1,2,4-TRIAZOLO[4,3-B]PYRIDO[3,2-D]PYRIDAZINE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This invention relates to new therapeutically useful heterocyclic compounds, to process for their preparation and to pharmaceutical compositions containing them.

It is known that inhibitors of phosphodiesterase 4 (PDE 4) are useful in the treatment of inflammatory and allergic processes such as asthma, non-steroidal antiinflammatory drugs-induced gastrointestinal damage and atopic dermatitis.

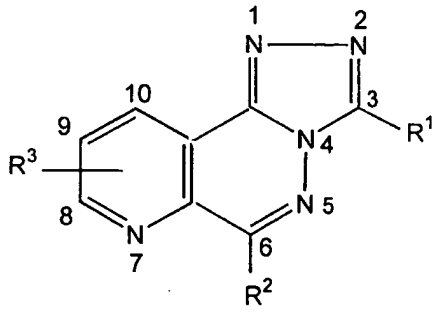
EP-A-85,840 discloses a series of triazolo-phthalazine derivatives of formula:



which are useful as anxiolytic agents.

We have now found that the presence of a pyridine ring instead of the benzo ring in the above structure, provides new compounds which inhibit cyclic phosphodiesterases, in particular type 4 cyclic phosphodiesterases and have a very low emetic activity (10-100 times less active than rolipram in inducing emesis in dogs).

Accordingly, the present invention provides a compound which is a heterocycle of formula (I):



(I)

wherein:

R^1 represents a hydrogen atom or a $-(CH_2)_m-Y$ group, wherein m is an integer from 0 to 4 and Y represents an alkyl, haloalkyl (preferably trifluoromethyl), alkoxy, alkoxycarbonyl, C_3-C_7 cycloalkyl, norbornyl (preferably 2-norbornyl) or phenylalkenyl group, or an aromatic group (preferably phenyl or pyridyl) which aromatic group Y may optionally be substituted by one or more halogen atoms;

R^2 represents an aromatic group (preferably phenyl, naphthyl or thienyl) which aromatic group may optionally be substituted by one or more halogen atoms or alkyl, alkoxy, C_3-C_6 cycloalkoxy, methylenedioxy, nitro, dialkylamino or trifluoromethyl groups; and

R^3 represents a hydrogen or halogen atom (preferably chloro) or an alkyl group,

and pharmaceutically acceptable salts thereof.

The alkyl, haloalkyl, alkenyl or alkynyl groups and moieties, such as in the alkoxy groups, mentioned in relation to the groups R^1 - R^3 in compounds of the invention are usually "lower" alkyl, that is containing up to 6 and particularly up to 4 carbon atoms, the hydrocarbon chain being branched or straight. Examples of alkyl groups and moieties are CH_3, C_2H_5, C_3H_7, i-C_3H_7, n-C_4H_9, i-C_4H_9, isoamyl and neopentyl.

When any of the groups, such as R^1 or R^2 has a chiral centre, the compounds of formula (I) exhibit optical isomerism and the isomers are within the scope of the present invention.

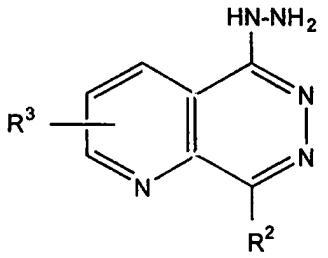
Examples of R^1 are the preferred alkyl groups mentioned above, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl and cyclopenthylmethyl.

Examples of R^2 are phenyl, 3-chlorophenyl, 4-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl and 3-nitrophenyl.

Examples of R^3 are hydrogen, alkyl or chloro, preferably in the 8- or 9- positions.

The most preferred compounds of the invention are 6-(4-fluorophenyl)-3-isobutyl-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine, 3-cyclopropylmethyl-6-(3-nitrophenyl)-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine, 3-cyclopropyl-6-phenyl-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine, and 3-cyclobutylmethyl-6-(3-nitrophenyl)-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine.

According to a further feature of the present invention, the heterocyclic compounds of formula (I) can be prepared from the corresponding hydrazine derivative of formula (II):



(II)

wherein

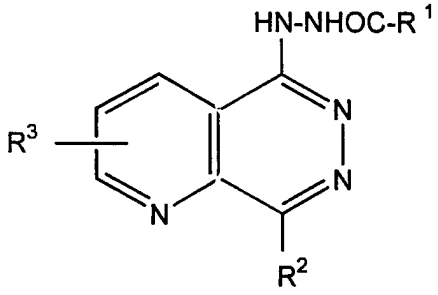
R^2 and R^3 are as defined above, by reaction with a reactive derivative of a carboxylic acid of the general

formula (III):

$$HOOC - R^1 \qquad \textbf{(III)}$$

wherein R^1 is as defined above. The reactive derivative of the said carboxylic acid may be, for example, a halide (preferably chloride), an anhydride or a mixed anhydride.

The reaction is preferably carried out in an inert organic solvent such as methylene chloride, dioxane or tetrahydrofuran, in the presence of an organic nitrogen-containing base, e.g. triethylamine and at a temperature between -10°C and +60°C. In the reaction, the corresponding hydrazide of general formula (IV) is first formed:

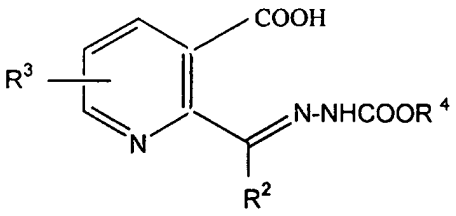


(IV)

wherein R^1, R^2 and R^3 are as defined above. A suspension of this hydrazide (IV) in an organic solvent such as dioxane, tetrahydrofuran, isopropanol or n-butanol, is heated, for example at the boiling point of the solvent, to give the corresponding heterocyclic compound of formula (I).

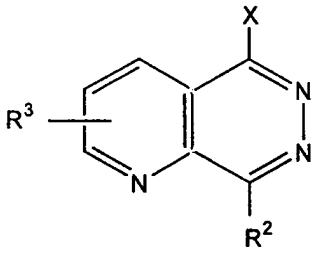
The hydrazine derivative of formula (II) may be prepared by:

1) reacting a hydrazone of formula (V):



(V)

wherein R^2 and R^3 are as defined above and R^4 is an alkyl group, with a phosphorus halide or phosphorus oxyhalide (preferably phosphorus oxychloride), to form the intermediate compound of formula (VI):



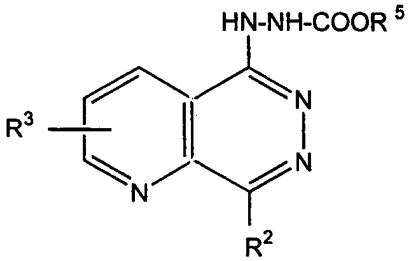
(VI)

wherein R^2 and R^3 are as defined above and X is a chlorine or bromine atom;

2) reacting compound (VI) with an alkyl carbazate (preferably t-butyl carbazate) of formula (VII):

$$H_2N\text{-}NH\text{-}COOR^5 \qquad \textbf{(VII)}$$

wherein R^5 is an alkyl group, to give the alkoxycarbonylhydrazine derivative (VIII):



(VIII)

wherein R^2, R^3 and R^5 are as defined above; and

3) treating compound (VIII) with hydrogen chloride in an anhydrous solvent as ethanol.

The reaction between the hydrazone of formula (V) and a phosphorus halide or phosphorus oxyhalide is carried out with an excess of reagent at a temperature from 80°C to 120°C, then removed the excess of reagent and poured into cold water. In this way the compound (VI) is obtained.

The reaction of (VI) with the alkyl carbazate of formula (VII) to obtain the corresponding alkoxycarbonylhydrazine derivative (VIII), is preferably carried out in the presence of an organic solvent as tetrahydrofuran or dioxan at a temperature of from 60°C to the boiling point of the reaction medium.

The alkoxycarbonylhydrazine derivative (VIII) may, for example, be transformed into the hydrazine derivative (II) at room temperature in hydrogen chloride-ethanol saturated solution.

The hydrazone derivatives of formula (V) are known compounds which can be prepared from the corresponding 2-acylnicotinic acid by known methods described in the literature.

The inhibition of cyclic nucleotide phosphodiesterase 4 from guinea-pig hearts was performed using 96-well microtiter plates as described by Verghese et al., (Molecular Pharmacology, 47, 1164-1171 (1995)).

The results from such test are shown in Table 1.

TABLE 1

Compound *	PDE4 IC_{50} (μM)
A	10
6	2
7	0.3
12	3
31	0.2
47	0.7
55	0.2
60	0.1
61	2
109	0.04
112	0.7
113	0.2

(*) See structures in Table 2.

Compound A is 3-isobutyl-6-phenyl-1,2,4-triazolo[3,4-a] phthalazine, a compound included in EP-A-85,840.

As it can be seen from Table 1, the compounds of formula (I) are cyclic phosphodiesterase inhibitors, in particular type 4 cyclic AMP phosphodiesterase inhibitors. The compounds are also capable of blocking the production of some pro-inflammatory cytokines such as, for example, TNFα. Thus, they can be used in the treatment of allergic, inflammatory and immunological diseases, as well as those diseases or conditions where the blockade of pro-inflammatory cytokines or the selective inhibition of PDE 4 could be of benefit.

These diseases states include asthma, rheumatoid

arthritis, osteoarthritis, osteoporosis, bone-formation disorders, glomerulonephritis, multiple sclerosis, Graves ophtalmopathy, myasthenia gravis, insulin-dependent diabetes mellitus, graft rejection, gastrointestinal disorders such as ulcerative colitis or Crohn disease, septic shock, adult distress respiratory syndrome, and skin diseases such as atopic dermatitis, contact dermatitis, acute dermatomyositis and psoriasis.

They can also be used as improvers of cerebrovascular function as well as in the treatment of other CNS related diseases such as dementia, Alzheimer's disease, depression, and as nootropic agents.

The compounds of the present invention are also of benefit when administered in combination with other drugs such as steroids and immunosuppressive agents, such as cyclosporin A, rapamycin or T-cell receptor blockers. In this case the administration of the compounds allows a reduction of the dosage of the other drugs, thus preventing the appearance of the undesired side effects associated with both steroids and immunosuppressants.

The compounds of the invention have also shown their efficacy in blocking, after preventive and/or curative treatment, the erosive and ulcerogenic effects induced by a variety of etiological agents, such as antiinflammatory drugs (steroidal or non-steroidal antiinflammatory agents), stress, ammonia, ethanol and concentrated acids. They can be used alone or in combination with antacids and/or antisecretory drugs in the preventive and/or curative treatment of gastrointestinal pathologies like drug-induced ulcers, peptic ulcers, H. Pylori-related ulcers, esophagitis and gastro-esophageal reflux disease.

They can also be used in the treatment of pathological situations where damage to the cells or tissues is produced

through conditions like anoxia or the production of an excess of free radicals. Examples of such beneficial effects are the protection of cardiac tissue after coronary artery occlusion or the prolongation of cell and tissue viability when the compounds of the invention are added to preserving solutions intended for storage of transplant organs or fluids such as blood or sperm. They are also of benefit on tissue repair and wound healing.

The present invention also provides a heterocyclic compound of formula (I) for use in a method of treatment of the human or animal body by therapy, particularly for use as a PDE 4 inhibitor or to block the production of a pro-inflammatory cytokine such as TNFα.

The present invention additionally provides a pharmaceutical composition which comprises, as active ingredient, at least one heterocyclic compound of formula (I), and a pharmaceutically acceptable carrier or diluent.

Preferably the compositions are in a form suitable for oral, inhalation, rectal, transdermal, nasal, topical or parenteral administration.

The pharmaceutically-acceptable carriers or diluents which are admixed with the active compound or compounds to form the compositions of this invention are well known per se and the actual excipients used depend inter alia on the intended method of administration of the compositions.

Compositions of this invention are preferably adapted for administration per os. The compositions for oral administration may take the form of tablets, capsules, lozenges or effervescent granules or liquid preparations such as elixirs, syrups or suspensions, all containing one or more compounds of the invention. Such preparations may be made by methods well known in the art, for instance by mixing the heterocyclic compound of formula (I) with the

pharmaceutically acceptable carrier or diluent.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents if desided. Tablets or capsules may conveniently contain from 1 to 100 mg and preferably from 5 to 50 mg of active ingredient. The compounds may also be incorporated into pellets coated with appropriate natural or synthetic polymers known in the art to produce sustained release characteristics or incorporated with polymers into tablet form to produce the same characteristics.

The liquid compositions adapted for oral use may be in the form of solutions, suspensions or aerosols. The solutions may be aqueous or aqueous-alcoholic solutions in association with, for example, sucrose or sorbitol to form a syrup. The suspensions may comprise an insoluble or microencapsulated form of an active compound of the invention in association with water and other acceptable solvents together with a suspending agent or flavouring agent.

Compositions for inhalation administration may be in the form of solutions, suspensions or micronized powder, contained in an appropriate inhaler.

Compositions for parenteral injection may be prepared, which may or may not be freeze-dried and which may be dissolved in water or an appropriate parenteral injection fluid.

In human therapy, the doses of the heterocyclic compound depend on the desired effect and duration of the treatment; adult doses are generally from 1mg to 100 mg per day. In general the physician will decide the posology, taking into account the age and weight of the patient being treated.

The following Examples further illustrate the invention.

EXAMPLE 1

a) A mixture of t-butoxycarbonylhydrazone of 2-benzoylnicotinic acid (45 g; 13.2 mols) in phosphorus oxychloride (500 ml) was boiled under reflux for one hour, then the excess of phosphorus oxychloride was removed under reduced pressure, the residue treated with ice-water and extracted twice with methylene chloride. The organic solution was washed with 4% sodium bicarbonate aqueous solution, with brine and after drying (Na_2SO_4), the solvent removed *in vacuo*. The obtained solid was collected with a mixture of diethyl ether-petrol ether 1:1 to give 5-chloro-8-phenylpyrido[2,3-d]pyridazine as a red solid, (25.4 g; 80% yield).

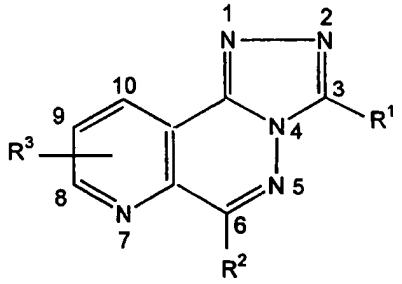
b) To a suspension of the above compound (18.2; 0.075 mols) in anhydrous tetrahydrofuran (180 ml), t-butyl carbazate (10.0 g; 0.075 mols) was added and the mixture was boiled under reflux for one hour. After cooling the crystallized solid was collected by filtration when 5-t-butoxycarbonylhydrazino-8-phenylpyrido[2,3-d]pyridazine was obtained (28.5 g). This compound was solved in ethanol (150 ml), hydrogen chloride in ethanol saturated solution (100 ml) was added and the resulting mixture stirred at room temperature for 15 hours. A solid was formed which was collected by filtration and washed with diethyl ether to give 5-hydrazino-8-phenylpyrido[2,3-d]pyridazine dihydrochloride (21.6 g; 92% yield).

c) To a suspension of 5-hydrazino-8-phenylpyrido[2,3-d]pyridazine dihydrochloride (1.24 g; 0.004 mols) in methylene chloride (30 ml), triethylamine (1.9 ml; 0.013 mols) was added, then stirred at room temperature for 15 minutes and pivaloyl chloride (0.5 ml; 0.0044 moles) slowly

added. After stirring at room temperature for two hours, water (30 ml) was added, the formed yellow solid, collected by filtration and washed with diethyl ether to give the intermediate hydrazide. This compound was suspended in n-butanol (30 ml), boiled under reflux for 15 hours and on cooling, crystallized a white solid which was collected by filtration and washed with diethyl ether. The obtained solid was purified by flash column chromatography with silica gel and methylene chloride-ethanol-ammonium hydroxide 200:8:1 as eluent. 3-t-butyl-6-phenyl-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine was obtained (0.83 g; 69% yield), m.p. 188.1 (determined by Differential Scanning Calorimetry, Perkin-Elmer DSC-7 (compound 8 in Table 2).

The heterocyclic compounds of formula (I) in Table 2 were prepared according to the processes disclosed in this Example, but with the appropriate starting materials.

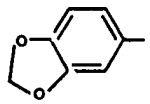
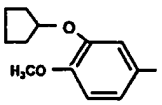
TABLE 2



Compound	R^1	R^2	R^3	m.p. °C
1	H	C_6H_5	H	215.8
2	CH_3	"	"	215.9
3	C_2H_5	"	"	194.1
4	C_3H_7	"	"	168.1
5	i-C_3H_7	"	"	176.8
6	n-C_4H_9	"	"	162.9
7	i-C_4H_9	"	"	179.7
8	t-C_4H_9	"	"	188.1
9	n-C_5H_{11}	"	"	137.4

Compound	R^1	R^2	R^3	m.p. °C
10	neopentyl	"	"	216.3
11	t-amyl	"	"	153
12	cyclopropyl	"	"	244.3
13	cyclobutyl	"	"	218
14	cyclopentyl	"	"	202.4
15	cyclohexyl	"	"	196.3
16	cyclopropyl-CH_2	"	"	195
17	cyclobutyl-CH_2	"	"	183
18	cyclopentyl-CH_2	"	"	193
19	cyclohexyl-CH_2	"	"	212.8
20	2-norbornyl-CH_2	"	"	217
21	C_6H_5	"	"	304.1
22	C_6H_5-CH_2	"	"	192
23	C_6H_5-CH_2CH_2	"	"	176
24	C_6H_5-CH=CH	"	"	278
25	CF_3	"	"	192.5
26	H_3CO-CH_2	"	"	159
27	2-ClC_6H_4	"	"	206
28	4-pyridyl	"	"	333.4
29	CH_3	4-FC_6H_4	"	276
30	n-C_4H_9	"	"	111
31	i-C_4H_9	"	"	135
32	t-C_4H_9	"	"	195
33	neopentyl	"	"	216
34	cyclopropyl	"	"	245
35	cyclohexyl	"	"	177
36	cyclopropyl-CH_2	"	"	160
37	cyclobutyl-CH_2	"	"	132
38	cyclopentyl-CH_2	"	"	162
39	2-norbornyl-CH_2	"	"	161
40	C_6H_5-CH=CH	"	"	272
41	C_2H_5OOC-CH_2	"	"	185
42	i-C_4H_9	3-FC_6H_4	"	147
43	neopentyl	"	"	190
44	cyclopropyl	"	"	222
45	cyclopropyl-CH_2	"	"	174
46	cyclobutyl-CH_2	"	"	139

Compound	R^1	R^2	R^3	m.p. °C
47	cyclopentyl-CH_2	"	"	145
48	i-C_4H_9	2-FC_6H_4	"	202
49	t-C_4H_9	"	"	212
50	neopentyl	"	"	235
51	cyclopropyl	"	"	262
52	cyclopropyl-CH_2	"	"	224
53	i-C_4H_9	4-ClC_6H_4	"	133
54	cyclopropyl	"	"	208
55	i-C_4H_9	3-ClC_6H_4	"	113
56	t-C_4H_9	"	"	160
57	neopentyl	"	"	177
58	t-amyl	"	"	150
59	cyclopropyl	"	"	189
60	cyclopropyl-CH_2	"	"	136
61	cyclobutyl-CH_2	"	"	156
62	cyclopentyl-CH_2	"	"	147
63	i-C_4H_9	2-ClC_6H_4	"	182
64	neopentyl	"	"	216
65	cyclopropyl	"	"	198
66	i-C_4H_9	4-BrC_6H_4	"	135
67	neopentyl	"	"	204
68	cyclopropyl	"	"	208
69	cyclopropyl-CH_2	"	"	140
70	cyclopentyl-CH_2	"	"	187
71	2-norbornyl-CH_2	"	"	174
72	i-C_4H_9	3-BrC_6H_4	"	152
73	t-C_4H_9	"	"	160
74	neopentyl	"	"	177
75	cyclopropyl	"	"	186
76	cyclopentyl-CH_2	"	"	143
77	i-C_4H_9	3,4-diClC_6H_3	"	143
78	neopentyl	"	"	215
79	i-C_4H_9	3-$CH_3C_6H_4$	"	119
80	cyclopropyl	"	"	206
81	i-C_4H_9	2-$CH_3C_6H_4$	"	147
82	neopentyl	"	"	191
83	cyclopropyl	"	"	200

Compound	R^1	R^2	R^3	m.p. °C
84	i-C_4H_9	3,4-di$CH_3C_6H_3$	"	165
85	neopentyl	"	"	184
86	cyclopropyl	"	"	182
87	cyclohexyl	"	"	211
88	cyclopentyl-CH_2	"	"	144
89	i-C_4H_9	3-$CF_3C_6H_4$	"	139
90	cyclopropyl	"	"	172
91	cyclopentyl-CH_2	"	"	141
92	i-C_4H_9	4-$CH_3OC_6H_4$	"	177
93	cyclopropyl	"	"	164
94	i-C_4H_9	3-$CH_3OC_6H_4$	"	119
95	neopentyl	"	"	155
96	cyclopropyl	"	"	192
97	i-C_4H_9	2-$CH_3OC_6H_4$	"	181
98	cyclopropyl	"	"	211
99	"	3,4-di$CH_3OC_6H_3$	"	177
100	i-C_4H_9		"	158
101	t-C_4H_9	"	"	251
102	neopentyl	"	"	208
103	cyclopropyl	"	"	208
104	i-C_4H_9		"	193
105	t-C_4H_9	"	"	210
106	neopentyl	"	"	219
107	cyclopropyl	"	"	162
108	i-C_3H_7	3-$NO_2C_6H_4$	"	176
109	i-C_4H_9	"	"	178
110	neopentyl	"	"	229
111	cyclopropyl	"	"	234
112	cyclopropyl-CH_2	"	"	164
113	cyclobutyl-CH_2	"	"	150
114	cyclopentyl-CH_2	"	"	183
115	cyclopropyl	3-$(CH_3)_2NC_6H_4$	"	213

Compound	R^1	R^2	R^3	m.p. °C
116	i-C_4H_9	2-naphthyl	"	140
117	cyclopropyl	"	"	212
118	i-C_4H_9	2-thienyl	"	196
119	cyclopropyl	"	"	214
120	i-C_4H_9	3-thienyl	"	166
121	cyclopropyl	"	"	183
122	i-C_4H_9	C_6H_5	8-H_3C	170
123	neopentyl	"	"	221
124	cyclopropyl	"	"	185
125	cyclopentyl-CH_2	"	"	163
126	2-norbornyl-CH_2	"	"	193
127	i-C_4H_9	"	9-Cl	174
128	cyclopropyl	"	"	149
129	cyclopropyl-CH_2	"	"	175
130	cyclopentyl-CH_2	"	"	175

The following Examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 2

3,000 inhalation-flasks each containing 40 mg of 3-t-butyl-6-phenyl-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine (active compound) were prepared as follows:

Active compound	120 g
Sorbitan trioleate	4 g
propellent q.s.	60 l

Procedure

The microcrystalline suspension prepared with these ingredients was introduced in the inhalation-flasks at a volume of 20 ml per flask with a filling machine. The flasks

were furnished with an appropriate valve which released 0.2 ml of suspension for each activation (0.4 mg of active compound).

EXAMPLE 3

15,000 capsules each containing 20 mg of 3-t-butyl-6-phenyl-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine (active compound) were prepared from the following formulation:

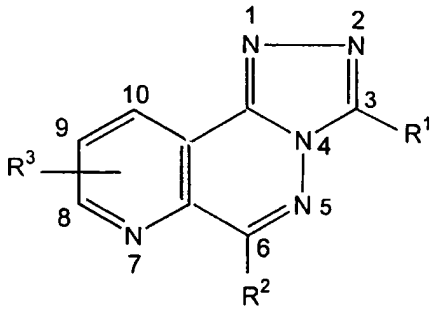
Active compound	300 g
Sodium carboxymethyl starch	330 g
Talc	195 g
Hydrogenated castor oil	165 g
Corn starch	495 g

Procedure

The above ingredients were sieved through a 60 mesh sieve, then mixed in a suitable mixer and filled into 15,000 gelatine capsules.

CLAIMS

1. A compound of formula (I)



(I)

wherein;

R^1 represents a hydrogen atom or a $-(CH_2)_m-Y$ group, wherein m is an integer from 0 to 4 and Y represents an alkyl, haloalkyl, alkoxy, alkoxycarbonyl, C_3-C_7 cycloalkyl, norbornyl or phenylalkenyl group, or an aromatic group which aromatic group Y may optionally be substituted by one or more halogen atoms;

R^2 represents an aromatic group which aromatic group may optionally be substituted by one or more halogen atoms or alkyl, alkoxy, C_3-C_6 cycloalkoxy, methylenedioxy, nitro, dialkylamino or trifluoromethyl groups; and

R^3 represents a hydrogen or halogen atom or an alkyl group,

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein the alkyl, haloalkyl and alkoxy groups have up to 6 carbon atoms, the alkoxycarbonyl groups have up to 7 carbon atoms and the phenylalkenyl groups have up to 12 carbon atoms.

3. A compound according to claim 1 or 2 wherein R^1 represents $-(CH_2)_m-Y$ wherein m is 0 or 1 and Y represents

C_{1-6} alkyl or C_{3-7} cycloalkyl.

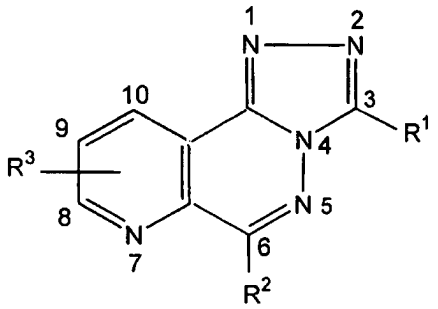
4. A compound according to any one of the preceding claims wherein R^2 represents a phenyl group, naphthyl group or thienyl group which group R^2 may optionally be substituted by one or more halogen atoms, methyl groups, methoxy groups, cyclopentoxy groups, nitro groups or dimethyl amino groups.

5. A compound according to claim 4 wherein R^2 represents a phenyl, 3-chlorophenyl, 4-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl or 3-nitrophenyl group.

6. A compound according to any one of the preceding claims wherein R^3 represents a hydrogen atom, a C_{1-6} alkyl group or a chlorine atom at the 8- or 9- position of the 1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine skeleton.

7. A compound according to claim 1 which is 6-(4-fluorophenyl)-3-isobutyl-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine, 3-cyclopropylmethyl-6-(3-nitrophenyl)-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine, 3-cyclopropyl-6-phenyl-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine and 3-cyclobutylmethyl-6-(3-nitrophenyl)-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine.

8. A process for preparing a compound of formula (I)



(I)

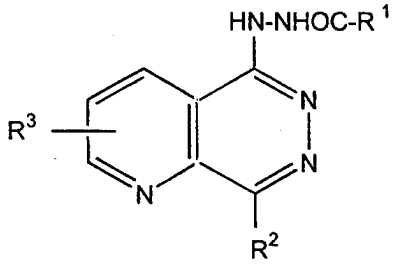
wherein;

R^1 represents a hydrogen atom or a $-(CH_2)_m-Y$ group, wherein m is an integer from 0 to 4 and Y represents an alkyl, haloalkyl, alkoxy, alkoxycarbonyl, C_3-C_7 cycloalkyl, norbornyl or phenylalkenyl group, or an aromatic group which aromatic group Y may optionally be substituted by one or more halogen atoms;

R^2 represents an aromatic group which aromatic group may optionally be substituted by one or more halogen atoms or alkyl, alkoxy, C_3-C_6 cycloalkoxy, methylenedioxy, nitro, dialkylamino or trifluoromethyl groups; and

R^3 represents a hydrogen or halogen atom or an alkyl group,

which process comprises formation of the 1,2,4-triazine ring present in formula (I) by cyclisation of a hydrazide of formula (IV)



(IV)

wherein R^1, R^2 and R^3 are as defined above.

9. A composition comprising a compound according to any one of claims 1 to 7 or pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable diluent or carrier.

10. A compound according to any one of claims 1 to 7 or pharmaceutically acceptable salt thereof or a composition according to claim 9 for use in a method of treatment of the

human or animal body.

11. Use of a compound according to any one of claims 1 to 7 or pharmaceutically acceptable salt thereof or a composition according to claim 9 for the manufacture of a medicament for the treatment of a condition whose known treatment is to inhibit phosphodiesterase 4 including allergic reaction and disease states, inflammation, ulcers and immunological disease.

12. A method of treating a condition whose known treatment is to inhibit phosphodiesterase 4 which comprises administering to a human or animal subject in need of such treatment an effective amount of compound according to any one of claims 1 to 7 or pharmaceutically acceptable salt thereof or a composition according to claim 9.

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/EP 98/04340

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/14 A61K31/50 //(C07D471/14,249:00,237:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 91, no. 17, 1979 Columbus, Ohio, US; abstract no. 133826z, ISHII ET AL.: "Inhibition of cyclic AMP phosphodiesterase activity by ecarazine hydrochloride, hydralazine and their metabolites" page 25; XP002052108 see abstract & YAKUGAKU ZASSHI, vol. 99, no. 5, 1979, pages 533-36, ---	1,11
A	WO 93 07146 A (SYNTEX) 15 April 1993 see claim 1; example 46 -----	1,11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 1998	20/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/ 04340

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10 to 12
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 10 to 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.